REMARKS

No amendments are currently made to the claims. Claims 82-84 and 87-94 are pending in the application. In light of the remarks below, Applicants respectfully request reconsideration and allowance of the pending claims.

The Rejection of the Claims as Obvious Should Be Withdrawn

Claims 82-84 and 87-94 have been rejected under 35 U.S.C. §103(a) as being obvious over Stomp *et al.* (1999, WO 99/07210) further in view of Wong *et al.* (*Plant Mol. Biol.* 20:81-93 (2002)), Buzby *et al.* (*Plant Cell* 2:805-814 (1990)) and Stiekema *et al.* (*Nucleic Acids Res.* 11-8051-8061 (1983)). Specifically, the Office Action asserts that it would have been obvious to modify the method of Stomp *et al.* by utilizing the 5′ leader sequence of Buzby *et al.* in light of the teaching of Wong *et al.* that an *Arabidopsis* RbcS 5′ leader sequence enhances translation. This rejection is respectfully traversed.

Applicants respectfully note that a *prima facie* case of obviousness under 35 U.S.C. §103(a) requires that a combination of references places the claimed subject matter in the public domain prior to Applicants' date of invention. See *In re Zenitz*, 333 F.2d 924, 142 USPQ 158 (C.C.P.A. 1964). Thus, establishing a *prima facie* case of obviousness requires that the cited references can be combined such that each and every element of the claimed invention is taught, explicitly or implicitly, by the references, and that a reasonable expectation of success exists in such a combination. As the Supreme Court recently clarified, obviousness under §103 requires consideration of the factors set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), including an analysis of the scope and content of the prior art and the difference between the claimed subject matter and the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 14 (2007).

With respect to the differences between the claimed subject matter and the prior art, the pending claims remain drawn to a duckweed plant culture or duckweed nodule culture, where the culture is stably transformed with one or more nucleotide sequences comprising a coding sequence for a biologically active polypeptide, an operably linked coding sequence for a signal peptide that directs secretion of the polypeptide, and an operably linked 5′ leader sequence

consisting of SEQ ID NO:16, which sets forth the 5′ leader of the *Lemna gibba* 5B RbcS gene. Applicants have discovered that substantial increases in recombinant protein expression can be achieved in duckweed by including the 5′ leader sequence set forth in SEQ ID NO:16 in the transformation construct. Applicants respectfully refer the Examiner to the specification at, for example, page 27, line 27, to page 29, line 4, and page 36, line 15, to page 37, line 6, in which Applicants demonstrate robust expression of biologically active polypeptide in stably transformed duckweed using the operably linked 5′ leader sequence consisting of SEQ ID NO:16. There is no requirement that the RbcS 5′ leader be operably linked to a sequence encoding a chloroplast transit peptide, or even a native transit peptide coding sequence, in order to achieve marked improvements in recombinant protein production. In fact, the claims require that the coding sequence for the biologically active polypeptide is operably linked to a signal peptide that directs secretion of the polypeptide, which is counter to the presence of an operably linked transit peptide coding sequence.

The discovery that substantial increases in recombinant protein expression can be achieved in duckweed by including the specific 5′ leader sequence set forth in SEQ ID NO:16 clearly is a surprising result that is not taught or suggested by the combination of Stomp *et al.*, Wong *et al.*, Buzby *et al.*, and Stiekema *et al.* For example, Stiekema *et al.* teach a *Lemna gibba* ribulose 1,5-bisphophate carboxylase small subunit transit peptide. Stomp *et al.* teach that this transit peptide can be used to target expression of a heterologous polypeptide to the chloroplast. Wong *et al.* teach that *in vivo* protein expression in stably transformed whole plants is dependent on both the RbcS 5′ leader sequence and the RbcS native transit peptide. See Wong *et al.* at page 88 and the paragraph spanning pages 89-90. Applicants respectfully submit that, upon reading the Wong *et al.* reference, one having ordinary skill in the art would not have been prompted to use a RbcS 5′ leader sequence in the absence of the native RbcS transit peptide coding sequence for heterologous protein expression. Furthermore, the skilled artisan would not have been motivated to combine the methods of Wong *et al.* with the teachings of Stomp *et al.*, Stiekema *et al.*, or Buzby *et al.* Motivation to use a 5′ leader sequence consisting of SEQ ID NO:16 in the absence of a RbcS transit peptide coding sequence arises from the present application and not by

any combination of the cited references. On this basis alone, the obviousness rejection should be withdrawn.

With respect to the Examiner's allegation that use of a duckweed 5′ leader sequence consisting of SEQ ID NO:16 is "an obvious choice" simply because the expression host is also duckweed, Applicants respectfully disagree. It is improper to dismiss an invention as obvious simply because the nucleotide sequences of the invention are derived from the same organism. An explicit rationale for why one having ordinary skill in the art would have combined the elements in the manner claimed must be set forth. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 14 (2007). "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (quoting *In re Kahn*, 441 F.3d 997, 998 (Fed. Cir. 2006)). As described above, Applicants discovered that SEQ ID NO:16 alone could greatly enhance protein expression in stably transformed duckweed plants, which was an unexpected result in light of the prior art teaching that a transit peptide is needed for a RbcS 5′ leader to enhance protein expression in plants.

Applicants also respectfully disagree with the Examiner's allegation that "variability in efficacy is not considered as being unpredictable." (Office Action at page 10). Variability in efficacy is evidence of unpredictability in the art where properties of an element (such as high or low protein expression levels) are not predictable *a priori*. Results of the transient expression and whole plant assays in Wong *et al.* demonstrate that the effect of a RbcS 5′ untranslated leader on heterologous protein expression is unpredictable. As Applicants noted in the previous Response, the Examiner has acknowledged that the use of 5' leader sequences, including 5′ leader sequences of RbcS genes from the same plant species, to enhance expression of heterologous proteins is an unpredictable art.

As discussed, the combined disclosures of Stomp *et al.*, Buzby *et al.*, Wong *et al.*, and Stiekema *et al.* provide no teaching, suggestion, or motivation that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does. Applicants, therefore, respectfully submit that claims 82-84 and 87-94 are not obvious over the cited references, either alone or in combination. In view of foregoing remarks,

as well as for all of the reasons of record, Applicants request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

Claims 82-84 and 87-94 have been rejected under 35 U.S.C. §103(a) as being obvious over Stomp *et al.* (1999, WO 99/07210) further in view of Wong *et al.* (*Plant Mol. Biol.* 20:81-93 (2002)), Buzby *et al.* (*Plant Cell* 2:805-814 (1990)), and Stiekema *et al.* (*Nucleic Acid Res.* 11-8051-8061 (1983)) in further view of Hein *et al.* (U.S. Patent No. 5,989,177). This rejection is respectfully traversed.

As noted above, the combined teachings of the Stomp *et al.*, Wong *et al.*, Buzby *et al.*, and Stiekema references fail to demonstrate or even suggest that the specific 5′ leader sequence set forth in SEQ ID NO:16 would be useful for markedly enhanced expression of biologically active polypeptides in duckweed, particularly when used in the absence of the native transit peptide coding sequence. The Hein *et al.* reference teaches the assembly of multimeric polypeptides such as secretory antibodies in transgenic plants. However, the Hein *et al.* reference does not provide the teaching that a 5′ leader consisting of SEQ ID NO:16 could be used in the absence of its transit peptide coding sequence to markedly enhance recombinant protein production in duckweed while decreasing culture time required to achieve these enhanced levels of expression.

In view of foregoing remarks, as well as for all of the reasons of record, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

Claims 82-84 and 87-94 have been rejected under 35 U.S.C. §103(a) as being obvious over Stomp *et al.* (1999, WO 99/07210) further in view of Wong *et al.* (*Plant Mol.Biol.* 20:81-93 (2002)), Buzby *et al.* (*Plant Cell* 2:805-814 (1990)), Stiekema *et al.* (*Nucleic Acid Res.* 11-8051-8061 (1983)), and Hein *et al.* (U.S. Patent No. 5,989,177) in further view of Yu *et al.* (U.S. Patent No. 5,460,952) and Park *et al.* (*J. Biol. Chem.* 272:6876-6881 (1997)). This rejection is respectfully traversed.

As noted above, the Stomp *et al.*, Wong *et al.*, Buzby *et al.*, Stiekema *et al.*, and Hein *et al.* references fail to demonstrate or even suggest that the specific 5′ leader sequence set forth in SEQ ID NO:16 would be useful for expression of biologically active polypeptides in duckweed,

particularly when used in absence of the native transit peptide coding sequence. The Yu *et al.* reference teaches a signal peptide for secretion of a protein into the media of plant cell cultures. Park *et al.* teach that a signal peptide from the rice α-amylase polypeptide can be recognized and processed by various expression systems. However, neither of these additional references provide the teaching that the 5′ leader of the RbcS 5B gene of *Lemna gibba* (SEQ ID NO:16) could be used in the absence of its transit peptide coding sequence to markedly enhance recombinant protein production in duckweed while decreasing culture time required to achieve these enhanced levels of expression.

In view of foregoing remarks, as well as for all of the reasons of record, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

Non-Statutory Obviousness-Type Double Patenting Rejections

Claims 82-84 and 87 stand rejected under the judicially created doctrine of obviousness-type double patenting as patentably indistinct from claims 16 and 17 of U.S. Patent No. 6,815,184 to Stomp *et al.* (hereinafter Stomp II) in view of Buzby *et al.* (1990, *The Plant Cell* 2:805-814), and Wong *et al.* (1992, *Plant Molecular Biology* 20:81-93). This rejection is respectfully traversed.

The pending claims are directed toward stably transformed duckweed plant or nodule cultures that are transformed with one or more nucleotide sequences comprising a coding sequence for a biologically active polypeptide, an operably linked coding sequence for a signal peptide, and an operably linked 5′ leader sequence, where the leader sequence consists of SEQ ID NO:16, which sets forth the 5′ leader of the *Lemna gibba* 5B RbcS gene. Claims 16 and 17 of Stomp II are respectively directed to a method of producing biologically active α-2b-interferon in a duckweed plant culture or a duckweed nodule culture and to the transformed duckweed plants produced thereby. Claims 16 and 17 of Stomp II do not teach the specific 5′ leader sequence set forth in SEQ ID NO:16. Buzby *et al.* set forth SEQ ID NO:16 as a subsequence of a much larger upstream sequence of the *Lemna gibba* 5B RbcS gene, but provide no teaching whatsoever as to the use of this subsequence as a translational enhancer sequence. As noted above, Wong *et al.* teach a 10-fold to 20-fold enhancement of expression, but it is only achieved with a construct

comprising **both** the RbcS 5′ untranslated leader and its native transit peptide coding sequence. Wong *et al.* also teach that the effect of a RbcS 5′ untranslated leader on heterologous protein expression is unpredictable. Given the combined teachings of these cited references, one of skill in the art had no expectation of success that SEQ ID NO:16 alone could be used in duckweed to significantly enhance heterologous protein production while decreasing culture time to achieve these increased production levels, particularly in the absence of the operably linked native transit peptide coding sequence.

In view of the foregoing remarks, as well as for all of the reasons of record, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 82-84 and 87-94 remain rejected under the judicially created doctrine of obviousness-type double patenting as patentably indistinct from claims 3, 8-10, 23, and 26-29 of commonly owned U.S. Patent Application No. 10/794,615 by Dickey *et al.* This application has now issued as U.S. Patent No. 7,632,983. At which time allowable subject matter is agreed upon in the case of the present application, Applicants will timely file the required terminal disclaimer and appropriate fee to address this double-patenting rejection.

Claims 82-84 and 87 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as patentably indistinct from claims 1-25 of U.S. Patent Application No. 11/778,480 by Stomp *et al.* (Stomp III) in view of Wong *et al.* (1992, *Plant Molecular Biology* 20:81-93) and Buzby *et al.* (1990, *The Plant Cell* 2:805-814). This rejection is respectfully traversed.

The pending claims are directed toward stably transformed duckweed plant or nodule cultures that are transformed with one or more nucleotide sequences comprising a coding sequence for a biologically active polypeptide, an operably linked coding sequence for a signal peptide, and an operably linked 5′ leader sequence, where the leader sequence consists of SEQ ID NO:16, which sets forth the 5′ leader of the *Lemna gibba* 5B RbcS gene. Claims 1-25 of Stomp III are directed to stably transformed duckweed plants that produce biologically active α-2b-interferon. Claims 1-25 of Stomp III do not teach the specific 5′ leader sequence set forth in

SEQ ID NO:16. Buzby *et al.* set forth SEQ ID NO:16 as a subsequence of a much larger upstream sequence of the *Lemna gibba* 5B RbcS gene, but provide no teaching whatsoever as to the use of this subsequence as a translational enhancer sequence. As noted above, Wong *et al.* teach a 10-fold to 20-fold enhancement of expression, but it is only achieved with a construct comprising **both** the RbcS 5′ untranslated leader and its native transit peptide coding sequence. Wong *et al.* also teach that the effect of a RbcS 5′ untranslated leader on heterologous protein expression is unpredictable. Given the combined teachings of these cited references, one of skill in the art had no expectation of success that SEQ ID NO:16 alone could be used in duckweed to significantly enhance heterologous protein production while decreasing culture time to achieve these increased production levels, particularly in the absence of the operably linked native transit peptide coding sequence.

In view of the foregoing remarks, as well as for all of the reasons of record, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the rejection of claims 82-84 and 87-94 under 35 U.S.C. § 103(a) and the obviousness-type double-patenting rejections are now overcome. Applicants further submit that this application is in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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